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 NEWS  6  Oct 27  DATA ELEMENTS TO BE REMOVED FROM JAPIO
 NEWS  7  Nov  8  Derwent World Patents Index: Technology Focus
                  To Be Added to Basic Index
 NEWS  8  Nov 24  PRINT FAX, SDI FAX NO LONGER AVAILABLE
 NEWS  9  Nov 24  STEREO BOND SEARCH PROBLEM WITH STN EXPRESS WITH
                  DISCOVER! 5.0 (WINDOWS ONLY)
 NEWS 10  Dec  2  Service during the transition to 2000

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                                                       ENTRY    SESSION
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=> s 35644-62-3/rn

L1             1 35644-62-3/RN

=> s 103742-76-3/rn

L2             1 103742-76-3/RN

=> file biosci

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FILE 'REGISTRY' ENTERED AT 11:58:29 ON 06 DEC 1999
L1 1 S 35644-62-3/RN
L2 1 S 103742-76-3/RN

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FILE 'ADISALERTS, ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, AQUASCI,
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHDS, CABA, CANCERLIT, CAPLUS,
CEABA, CEN, CIN, CONFSCI, CROPB, CROPU, DGENE, DRUGB, DRUGLAUNCH,
DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, ...' ENTERED AT
11:59:44 ON 06 DEC 1999

=> s l1 or l2

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  39 FILES SEARCHED...
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L3          18 L1 OR L2

=> s ment#### or ment-ac## or ment ac
<------User Break------>
u
SEARCH ENDED BY USER
SEARCH ENDED BY USER

=> s (ment####) or (ment-ac##) or (ment ac)

   9 FILES SEARCHED...
  15 FILES SEARCHED...
  23 FILES SEARCHED...
  28 FILES SEARCHED...
<------User Break------>
u
SEARCH ENDED BY USER

=> s  (ment-ac##) or (ment ac)

  12 FILES SEARCHED...
  27 FILES SEARCHED...
  34 FILES SEARCHED...
  43 FILES SEARCHED...
  49 FILES SEARCHED...
L4          40 (MENT-AC##) OR (MENT AC)

=> s methyl? (5a) nortestosterone?

   7 FILES SEARCHED...
  12 FILES SEARCHED...
  19 FILES SEARCHED...
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  25 FILES SEARCHED...
  31 FILES SEARCHED...
  38 FILES SEARCHED...
  48 FILES SEARCHED...
L5        1000 METHYL? (5A) NORTESTOSTERONE?

=> s testosterone# or fsh or lh

  25 FILES SEARCHED...
  49 FILES SEARCHED...
L6      586275 TESTOSTERONE# OR FSH OR LH

=> s contracepti? or steril?

  25 FILES SEARCHED...
L7      682228 CONTRACEPTI? OR STERIL?

=> s (l3 or l4) and l7

  39 FILES SEARCHED...
L8          16 (L3 OR L4) AND L7

=> s l8 and l6

  37 FILES SEARCHED...
L9          11 L8 AND L6

=> dup rem l9

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, BIOCOMMERCE, DGENE, DRUGLAUNCH,
DRUGMONOG2, FOREGE, GENBANK, KOSMET, PHAR'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L9
L10           6 DUP REM L9 (5 DUPLICATES REMOVED)

=> d bib,ab,kwic l10 1-6


L10 ANSWER 1 OF 6  USPATFULL
AN    1999:110309  USPATFULL
TI    Androgenic steroid compounds and a method of making and using the same
IN    Cook, C. Edgar, Staunton, VA, United States
      Kepler, John A., Raleigh, NC, United States
      Lee, Yue-Wei, Chapel Hill, NC, United States
      Wani, Mansukh C., Durham, NC, United States
PA    Research Triangle Institute, Research Triangle Park, NC, United States
      (U.S. corporation)
PI    US 5952319, 19990914
AI    US 1997-979369  19971126 (8)
DT    Utility
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Badio, Barbara
LREP  Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
CLMN  Number of Claims: 25
ECL   Exemplary Claim: 1
DRWN  No Drawings
LN.CNT 1048
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB    An androgenic steroid compound of the formula: ##STR1## wherein: X, Y,
      Z, R.sup.1, R.sup.2, R.sup.3, R.sup.5 and R.sup.6 are as defined
herein.
SUMM  Testosterone is the principal male hormone and is required for
      the development and maintenance of secondary sexual characteristics,
      libido and spermatogenesis. Testosterone also has anabolic
      properties, in promoting in muscle growth and maintenance. Lower than
      normal testosterone levels in men have been associated with
```

low energy, frailty, depression, decreased libido, weakness, lethargy, loss of lean body and bone mass and impotence. A second androgen, dihydrotestosterone (DHT), is produced from **testosterone**. DHT is a potent androgen. It is believed to be responsible for prostate growth and inhibitors of the enzyme that. . .

SUMM **Testosterone** is rapidly metabolized in the body. Since the liver metabolizes most orally administered **testosterone** before it reaches the systemic blood circulation, large oral doses are necessary in order to have the desired effect. To. . . the same by intramuscular injection, nevertheless, doses of 200 mg must still be given at weekly or bi-weekly intervals. Although **testosterone** can be administered by skin patch, large patches must be used due to low

activity and rapid metabolism. Recently, a. . .

SUMM Hence, a need exists for an androgenic compound that has enhanced potency relative to **testosterone**, which would permit more facile procedures for administration, such as the use of smaller skin patches, implantable devices or even. . .

SUMM In accordance with the present invention, androgenic steroid compounds are provided which exhibit enhanced activity relative to **testosterone**.

SUMM In accordance with the present invention, certain androgenic steroid compounds are provided which exhibit surprisingly enhanced activity relative to **testosterone**. Due to the enhanced potency of the present compounds, their administration is quite facile. For example, by

virtue of the. . .

DETD . . . such therapy. Other conditions or treatments may also require the use of androgenic compounds. For example, one approach to male **contraception** entails the use of **testosterone** or esters thereof to suppress gonadotrophin production, thereby achieving azoospermia or oligospermia. Perhaps more practical in achieving azoospermia is the use of **testosterone** in combination with progestins, where the **testosterone** both contributes to the **contraceptive** effect and also replaces the otherwise suppressed endogeneous androgens. Administration of agonists or preferably antagonists of gonadotophin releasing hormone results in decreased sperm

production, but also suppresses **testosterone** production. Thus, **testosterone** or other androgen must be given to make up the deficit. Antiestrogens also cause infertility in male animals. Their use. . . addition to or supplementation of endogenous androgenic hormones. Due to the enhanced potency of the present compounds as compared to **testosterone**, however, the former can be administered in much lower doses than the latter, which makes the administration of the present. . .

DETD . . . are leuprolide acetate (agonist) and cetrorelix (antagonist). An example of an antiestrogen is 7.alpha.-(9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl)estra-1,3,5(10)-triene-3,17.beta.-diol. Examples of other anabolic steroids are **testosterone**, oxandrolone, nandrolone and fluoxymesterone. However, any progestin, analog or gonadotrophin releasing hormone, antiestrogen or other anabolic steroid may be used. . .

DETD Androgenic Activity was also evaluated using subcutaneous administration

to immature castrated male rats (**Testosterone**=100).

DETD . . . 1) and of the greater potency and longer duration of action of the enanthate ester of 7.alpha.,11.beta.-dimethyl-19-nortestosterone as compared with **testosterone** enanthate (See Table 2).

DETD . . . *Relative binding (Dihydrotestosterone = 100) to androgen receptor from rat ventral prostate

.sup.## Subcutaneous administration to immature castrated male rats (**Testosterone** = 100)

**Relative binding (Estradiol = 100) to estrogen receptor from immature

female rat uterus
.sub.$ Subcutaneous administration to immature. . .
DETD . . . Weight (%
Weight (%

Compound	Substituents on 19-nortestosterone: 7.alpha. 11.beta. Other	Dose	after change from control)	after change from control)	after change from control)
Testosterone enanthate (0.6 mg)	10-CH.sub.3 -Enanthate ester	1	0%	452%	409%
		2	6%	318%	339%
		4	-7%	281%	291%
		6	0%. . .		

IT 3764-87-2P, 7.alpha.-Methyl-19-nortestosterone 31022-20-5P
35644-62-3P 226066-52-0P 226066-53-1P 226066-55-3P
226066-56-4P 226066-57-5P 226066-58-6P 226066-59-7P
(synthesis and androgenic activity of steroid compds.)

L10 ANSWER 2 OF 6 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 1
AN 1999316774 EMBASE
TI Gonadotrophin and **testosterone** suppression by 7.alpha.-methyl-19-nortestosterone acetate administered by subdermal implant to healthy men.
AU Noe G.; Suvisaari J.; Martin C.; Moo-Young A.J.; Sundaram K.; Saleh S.I.; Quintero E.; Croxatto H.B.; Lahteenmaki P.
CS G. Noe, Inst. Chileno Medicina Reproductiva, Casilla 96, Santiago, Chile
SO Human Reproduction, (1999) 14/9 (2200-2206).
Refs: 20
ISSN: 0268-1161 CODEN: HUREEE
CY United Kingdom
DT Journal; Article
FS 003 Endocrinology
006 Internal Medicine
010 Obstetrics and Gynecology
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The synthetic androgen 7.alpha.-methyl-19 nortestosterone (MENT) is a potent suppressor of gonadotrophin that has several advantages for long term administration to normal or hypoandrogenic men. The aim of this study was to examine MENT serum concentrations following subdermal insertion of MENT acetate (**MENT Ac**) implants and their effects on gonadotrophins, **testosterone**, dihydrotestosterone (DHT), sex hormone-binding globulin, prostate specific antigen and insulin-like growth factor-1 serum concentrations in normal men. A total of 45 healthy men were recruited at three clinics. Each subject received one, two or four implants for 28 days. Serum samples were obtained before insertion and on days 8, 15, 22, 29, 36 and 43 after implant insertion. The average daily dose delivered in vivo by one implant was .apprx.500 .mu.g. One, two or four **MENT Ac** implants produced dose dependent and sustained serum MENT concentrations for the entire duration of treatment of 0.7 .+-. 0.1, 1.2 .+-. 0.1 and 2.0 .+-. 0.1 nmol/l respectively. This

treatment induced a dose dependent decrease in gonadotrophin and androgen serum levels. Two and four implants induced maximal suppression that was maintained throughout treatment and was completely reversed after removal of the implants. The mean decreases were 93 .+-. 1% for **testosterone**, 80 .+-. 3% for DHT, 97 .+-. 1% for luteinizing hormone and 95 .+-. 1% for follicle stimulating hormone. No serious adverse reactions were reported by the volunteers and no consistent changes in clinical chemistry and haematology were found. These results indicate that **MENT Ac** implants are an efficient way of MENT administration and confirm the potent gonadotrophin and androgen suppressive effect of this drug.

TI Gonadotrophin and **testosterone** suppression by 7.alpha.-methyl-19-nortestosterone acetate administered by subdermal implant to healthy men.

AB . . . or hypoandrogenic men. The aim of this study was to examine MENT serum concentrations following subdermal insertion of MENT acetate (**MENT Ac**) implants and their effects on gonadotrophins, **testosterone**, dihydrotestosterone (DHT), sex hormone-binding globulin, prostate specific antigen and insulin-like growth factor-1 serum concentrations in normal men. A total of. . . after implant insertion. The average daily dose delivered in vivo by one implant was .apprx.500 .mu.g. One, two or four **MENT Ac** implants produced dose dependent and sustained serum MENT concentrations for the entire duration of treatment of 0.7 .+-. 0.1, 1.2. . . maintained throughout treatment and was completely reversed after removal of the implants. The mean decreases were 93 .+-. 1% for **testosterone**, 80 .+-. 3% for DHT, 97 .+-. 1% for luteinizing hormone and 95 .+-. 1% for follicle stimulating hormone. No. . . were reported by the volunteers and no consistent changes in clinical chemistry and haematology were found. These results indicate that **MENT Ac** implants are an efficient way of MENT administration and confirm the potent gonadotrophin and androgen suppressive effect of this drug.

CT Medical Descriptors:
drug blood level
dose response
sex hormone determination
drug withdrawal
side effect
contraception
human
male
human experiment
normal human
adult
subcutaneous drug administration
article
*gonadotropin: EC, endogenous compound
***testosterone: EC, endogenous compound**
*nandrolone derivative: AE, adverse drug reaction
*nandrolone derivative: AD, drug administration
*nandrolone derivative: CR, drug concentration
*nandrolone derivative: DO, drug dose
*nandrolone. . .

RN (gonadotropin) 63231-54-9; (**testosterone**) 58-22-0; (androstanolone) 521-18-6; (somatomedin c) 67763-96-6; (follitropin) 9002-68-0; (luteinizing hormone) 39341-83-8, 9002-67-9

L10 ANSWER 3 OF 6 IFIPAT COPYRIGHT 1999 IFI DUPLICATE 2

AN 2959778 IFIPAT;IFIUDB;IFICDB

TI MALE **CONTRACEPTIVE** IMPLANT; ETHYLENE-VINYL ACETATE COPOLYMER, MEMBRANES, **STERILLANT** FOR DOSAGE

INF Moo-Young, Alfred J., Hastings-on-Hudson, NY
Saleh, Saleh I., Queens, NY

IN Moo-Young Alfred J; Saleh Saleh I
PAF The Population Council, Center for Biomedical Research, New York, NY
PA Population Council Inc The (5875)
EXNAM Azpuru, Carlos
AG Lerner, David, Littenberg, Krumholz & Mentlik
PI US 5733565 19980331
AI US 1996-606063 19960223
XPD 23 Feb 2016
FI US 5733565 19980331
DT UTILITY; CERTIFICATE OF CORRECTION
CDAT 23 Jun 1998
FS CHEMICAL
MRN 007984 MFN: 0534
CLMN 36
GI 5 Drawing Sheet(s), 7 Figure(s).
AB The present invention relates to implantable male **contraceptive** devices. An ethylene vinyl acetate copolymer based implant is described for delivery of an androgen and a system including an ethylene vinyl acetate copolymer based implant as well as a second implant are described for the administration of both androgen and a **sterilitant**. These implants may be used to provide **contraception** for men, as well as, for hormone therapy, treatment of enlarged prostate and other aliments.
TI MALE **CONTRACEPTIVE** IMPLANT; ETHYLENE-VINYL ACETATE COPOLYMER, MEMBRANES, **STERILLANT** FOR DOSAGE
AB The present invention relates to implantable male **contraceptive** devices. An ethylene vinyl acetate copolymer based implant is described for delivery of an androgen and a system including an. . . acetate copolymer based implant as well as a second implant are described for the administration of both androgen and a **sterilitant**. These implants may be used to provide **contraception** for men, as well as, for hormone therapy, treatment of enlarged prostate and other aliments.
ECLM . . . formed of a second ethylene vinyl acetate copolymer; and a second implant intended for subcutaneous or local administration of a **sterilitant**, said second implant including said **sterilitant** in an amount sufficient to provide for the daily dose of a pharmaceutically effective amount of said **sterilitant** over said predetermined time.
ACLM . . . cooperative size and shape and are designed such that each releases a pharmaceutically complementary amount of said androgen and said **sterilitant**; so as to provide treatment to a patient in need thereof.
7. The implantable system of claim 1, wherein said androgen is selected from the group consisting of MENT, **MENT Ac**, **testosterone**, methandroil, oxymetholone, methandienone, oxymesterone, nondrolone phenylpropionate, norethandrolone and pharmaceutically acceptable esters thereof.
9. The implantable system of claim 7, wherein said androgen is **MENT Ac**.
16. The implantable system of claim 1, wherein said second implant includes a biocompatible, non-biodegradable, water-swellable, water-insoluble, hydrophilic cartridge of. . . biocompatible, non-biodegradable, water-swellable, water-insoluble, hydrophilic polymer having an equilibrium water content value greater than that of the cartridge; with said **sterilitant** contained in a reservoir disposed within said cartridge.
18. The implantable system of claim 16, wherein said **sterilitant** is provided in an amount of between about 5 mg and about 50 mg.
19. The implantable system of claim 1, wherein said **sterilitant** is LHRH or an LHRH analog.
20. The implantable system of claim 19, wherein said **sterilitant** is LHRH or an LHRH analog.

22. The implant of claim 21, wherein said androgen is selected from the group consisting of MENT, **MENT Ac**, **testosterone**; esters of **testosterone**, methandroil, oxymetholone, methandienone, oxymesterone, nondrolone phenylpropionate and norethandrolone.

24. The implant of claim 22, wherein said androgen is **MENT Ac**.

33. A pharmaceutical kit comprising: a first implant intended for subcutaneous or local administration of an androgen, a second implant intended for a subcutaneous or local administration of a **sterilitant**, said first implant and said second implant having a cooperative size and shape and being designed such that each release a pharmaceutically complementary amount of said androgen and said **sterilitant** to a patient in need of treatment, said first implant and said second implant being loaded in a delivery means. . .

35. The kit of claim 34 wherein said second implant includes said **sterilitant** in an amount sufficient to provide for the daily dose of a pharmaceutically effective amount of said **sterilitant** over said predetermined time.

L10 ANSWER 4 OF 6 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 3
AN 1997:451983 BIOSIS
DN PREV199799751186
TI Pharmacokinetics of 7-alpha-methyl-19-nortestosterone in men and cynomolgus monkeys.
AU Kumar, Narender; Suvisaari, Janne; Tsong, Yun-Yen; Aguillaume, Claude; Bardin, C. Wayne; Lahteenmaki, Pekka; Sundaram, Kalyan (1)
CS (1) Cent. Biomed. Res., Population Council, 1230 York Ave., New York, NY 10021 USA
SO Journal of Andrology, (1997) Vol. 18, No. 4, pp. 352-358.
ISSN: 0196-3635.
DT Article
LA English
AB **Testosterone** and its esters are widely used for androgen replacement therapy. In the prostate, **testosterone** is 5-alpha-reduced to dihydrotestosterone (DHT), which leads to an amplification of its stimulatory activity in this and other tissues that have significant 5-alpha-reductase activity. While this amplification is essential during fetal development, it has potentially undesirable consequences during adult life. 7-alpha-Methyl-19-nortestosterone (MENT) is a potent synthetic androgen that does not undergo 5-alpha reduction and is therefore being investigated for long-term clinical use because it is expected to be less stimulatory to the prostate. Since we anticipate using MENT acetate (**MENT Ac**) rather than MENT as the form of this androgen in humans, the bioavailability of MENT following the administration of MENT and **MENT Ac** was investigated in cynomolgus monkeys. Equimolar concentrations of MENT or **MENT Ac** were administered as a continuous subcutaneous infusion via Alzet osmotic pumps. Serum MENT levels were measured by radioimmunoassay (RIA) in blood samples collected daily for 4 days during steady state. The serum MENT levels were not significantly different in the two groups (11.3 +- 1.6 vs. 13.1 +- 1.2 nmol/L). This suggested that **MENT Ac** was rapidly converted to MENT in circulation. The hydrolysis of **MENT Ac** to MENT was confirmed by the in vitro incubation of **MENT Ac** with blood or plasma and the demonstration of MENT in products following separation by high-performance liquid chromatography (HPLC). Following the demonstration of the safety of **MENT Ac** in subchronic toxicity studies in rats and rabbits, a pharmacokinetic study was performed in men. In normal men, a single intravenous bolus of 500 mu-g of MENT led to peak serum MENT levels

at 3 minutes after dosing (when the first samples were collected), followed by an exponential decline, reaching undetectable levels by 180 minutes. The average terminal half-life and the metabolic clearance rate (MCR) were calculated to be 40 minutes and 2,360 L/day, respectively. The results of the pharmacokinetic studies show that in both men and monkeys, the MCR of MENT is much faster than the values reported for **testosterone**. The faster MCR can be attributed, in part, to the finding that, in contrast to **testosterone**, MENT showed no binding to sex hormone binding globulin (SHBG).

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IT Miscellaneous Descriptors
ENDOCRINE SYSTEM; MALE; MALE **CONTRACEPTION**; METABOLIC CLEARANCE RATE; METABOLISM; REPRODUCTIVE SYSTEM; SEX HORMONE BINDING GLOBULIN; 7-ALPHA-METHYL-19-NORTESTOSTERONE

L10 ANSWER 5 OF 6 USPATFULL
AN 88:77512 USPATFULL
TI 17 a .beta.-hydroxy-7 .alpha.-methyl-d-homo-19-norandrost-4,16-diene-3-one and the 17-esters thereof: methods of preparation and uses
IN Tanabe, Masato, Palo Alto, CA, United States
Crowe, David F., Yreka, CA, United States
Detre, George, San Jose, CA, United States
Peters, Richard H., San Jose, CA, United States
Avery, Mitchell A.g34, Palo Alto, CA, United States
PA SRI International, Menlo Park, CA, United States (U.S. corporation)
PI US 4788218 19881129
AI US 1986-856386 19860428 (6)
RLI Continuation-in-part of Ser. No. US 1984-612415, filed on 21 May 1984, now abandoned
DT Utility
EXNAM Primary Examiner: Shippen, Michael L.
LREP Ciotti & Murashige, Irell & Manella
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1273

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel compounds having the general formula: ##STR1## wherein: R.sup.1 is

hydrogen or an acyl substituent of the formula:

--(C.dbd.O)--R.sup.2

wherein:

R.sup.2 is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkylene, haloalkyl, aryl, haloaryl or arylalkylene are described. These compounds have both gonadotropic and antigonadotropic properties depending upon the dosage level, and are therefore useful in therapy in the control of male fertility in mammals, particularly in human beings. These compounds combine gonadotropic, antigonadotropic and androgenic properties in the same compound. Their use with LHRH antagonists on male fertility control is also disclosed.

SUMM The lack of a similar **contraceptive** "pill" for males has stimulated research in male fertility control. Male fertility is a function of spermatogenesis. Since spermatogenesis is. . .

SUMM . . . the International Journal of Andrology, Supplement 2, pp 147-154, (1978), that the .DELTA..sup.16 -D-homo-19-nortestosterone propionate was 50% as active as **testosterone** propionate as an androgen, and was 10 times as potent as **testosterone** propionate in decreasing testicular weight in rats when administered subcutaneously. Newman also reported, in contrast to the present invention, that all orally active androgens are 17-alkyl derivatives of **testosterone**. One such material, 17-methyltestosterone, is marketed by Brown Pharmaceutical Company. In the Physician's Desk Reference, 39th Ed (1985) it is. . . benign liver cysts, and highly vascularized liver tumors which can lead to fatal hemorrrhages. Thus, an alternative to these 17-alkyl **testosterones** would be desirable for oral androgen therapy.

SUMM . . . al., in the International Journal of Andrology, Vol. 5, (1982) pp 413-424, compare antispermatogenic effects of a new D-homosteroid and **testosterone** in rabbits. They conclude that 18.beta.-hydroxy-18.alpha.-methyl-16.alpha.,17.alpha.-methylene-D-homo-5.alpha.-androstane-3-one surpresses spermatogensis and increases accessory sex gland weights at doses when **testosterone** is still ineffective. Thus in rabbits, the new steroid appears to be a more potent androgen than **testosterone** but an association between antigonadotropic and androgenic properties is not observed.

SUMM . . . in the Journal of Steroid Biochemistry, Vol. 13, pp 1261-1264, published in 1980 compares the tropic and serum leutinizing hormone (**LH**)-decreasing effects of **testosterone**, 19-nortestosterone, 5.alpha.-dihydrotestosterone and their corresponding D-homo-.DELTA..sup.16 analogs in rats. He concludes that the shape of the D ring is important. . . 5.alpha.-reductase to act on these compounds. Further, 5.alpha. reduction at the 5-position is most important for the negative action on **LH** release, less important for tropic activity on accessory sex organs, and of minor importance for the myotropic (anabolic) activity.

SUMM Oral androgen activity has also been reported by Segaloff for 7-methyl analogs of **testosterone** and 17-acyl esters of **testosterone**, compounds of different ring structure than the norandostrones of this invention.

SUMM . . . the case of the '918 materials having a 10 position methyl. These references disclose their materials to be useful as **contraceptives** and regulators of the female menstral cycle

('476) and as subquetaneous androgens (having 3 times the activity of **testosterone** which as will be shown the present materials are as much as 40 or more times as active as **testosterone**). Oral activity is not disclosed.

SUMM (a) reacting 6-ene **testosterone** with lithium dimethyl copper to produce the 7.alpha.-methyl-derivative;

SUMM . . . of the invention function as potent oral androgens and maintain male libido without liver toxicity. LHRH antagonists are attractive male **contraceptive** agents which have the side effect of decreasing male libido. Representative LHRH antagonists are described in the literature. See, for example, the book LHRH and Its Analogs, **Contraceptive** and Therapeutic Applications, B. H. Vickery et al, eds, MTP Press Limited, Lancaster, PA, 1984 ("Vickery et al").

SUMM . . . antigonado-tropic effect and, in the control of spermatogenesis in male mammals. These compounds are in large doses, useful in male **contraception**, in a mammal, particularly a human being, while maintaining the male libido. In smaller doses, a paradoxical result is observed. . .

SUMM . . . formula I where R.sup.1 is ethyl, when tested in rats, was found to have 40 times the androgenic activity of **testosterone** via subcutaneous injection and 6 times the activity of 17.alpha.-methyltestosterone when orally administered. Further, the androgenic effect of this compound when orally administered was 6 times the effect for methyl **testosterone**.

SUMM . . . when orally administered. These compounds appear to have antigonadoptropic activity which interferes with spermatogenesis at the testicular level by supressing **testosterone** synthesis via feedback control and also have androgenic activity to maintain libido and secondary sex characteristics.

DETD

Ingredients

Active ingredient	0.2 g
KH.sub.2 PO.sub.4 buffer (0.4 M solution)	2 ml
KOH (1 N)	q.s. to pH 7
water (distilled, **sterile**)	q.s. to 20 ml

DETD . . . with results listed in publications and patents for other androgenic materials. To facilitate comparison, all values were compared to 17.alpha.-methyl **testosterone** which was arbitrarily assigned a value of 1.0 for oral and subcutaneous androgenic activity. The results of this comparison are. . . have markedly higher oral activity than any other norandrostone materials. The only other material having similar activity being a the **testosterone** material of Segaloff. These results also point out another unexpected property of the present compounds. While they do have outstanding. . .

DETD TABLE 1

	ANDROGENIC ACTIVITY(RAT)		
COMPOUND	ORAL	SUBQ	RBA
Compounds of this invention			
##STR7##	5	40	8%
##STR8##	4	20-40 (Est)	2%
Testosterone	0.03	1	20%

##STR9##
17-Methyltestosterone 1 1 40%
##STR10##
Dihydrotestosterone 0.1 100%
##STR11##
Segaloff Compound 5.7 100.+-. --
##STR12##
Segaloff Compound 2.5 20
##STR13##
Furst. . .
IT 103742-75-2P **103742-76-3P** 103742-77-4P 103742-78-5P
(prepn. of, as androgen, contraceptive, etc.)

L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1986:515282 CAPLUS
DN 105:115282
TI 17.beta.-Hydroxy-7.alpha.-methyl-D-homo-19-norandrosta-4,16-dien-3-one and
17-esters
IN Tanabe, Masato; Crowe, David Franklin; Detre, George Stephen
PA SRI International, USA
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 8505361	A1	19851205	WO 1985-US609	19850408
W: DK, FI, JP, NO				
RW: AT, BE, CH, DE, FR, GB, IT, NL, SE				
EP 182808	A1	19860604	EP 1985-902235	19850408
R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE				
JP 61502186	T2	19861002	JP 1985-501806	19850408
DK 8600272	A	19860120	DK 1986-272	19860120
NO 8600177	A	19860120	NO 1986-177	19860120
FI 8600253	A	19860120	FI 1986-253	19860120

PRAI US 1984-612415 19840521
WO 1985-US609 19850408

AB The title steroids (I; R = H, acyl) are prepd. as male fertility-control agents, esp. for humans (formulations given). Thus, 7.alpha.-methylestrone was 3-O-methylated and treated with Me3SiCN to give the silylated C-17 cyanohydrin, which was reduced by LiAlH4 to the 17-(aminomethyl)-17-hydroxy deriv. Tiffeneau-Demjanov ring expansion of the latter gave the D-homoestrone deriv. II, which was dehydrogenated at C-16(C-17), reduced (LiAlH4, Li-NH3), and hydrolyzed to give I (R = H). Acylation of the alc. with (EtCO)2O gave I (R = COEt) (III). In rats, III had 40 times the androgenic activity of **testosterone** (s.c.), and 6 times the activity of 17.alpha.-methyltestosterone (orally). The effect of I on spermatogenesis is dosage-dependent (no data).
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IT **Contraceptives**
(male, homonorandrostadienones)
IT 103742-75-2P **103742-76-3P** 103742-77-4P 103742-78-5P
103742-79-6P 103742-80-9P 103742-81-0P 103742-83-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as male fertility-control agent)

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=> file stnguide

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   116.80     117.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.54      -0.54

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COPYRIGHT (C) 1999 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec  3, 1999 (19991203/UP).

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=> LOG H

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.00     117.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -0.54

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:15:09 ON 06 DEC 1999
Connection closed by remote host
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L10 ANSWER 4 OF 6 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 3
AN 1997:451983 BIOSIS
DN PREV199799751186
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